The USC*PACK PC Programs for NPEM Population Pharmacokinetic Modeling, "Multiple Model" Design of Dosage Regimens, and Adaptive Control of Dosage Regimens. A SCAMC Demonstration, November 1993.

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NEW MULTICOMPARTMENT NON - PARAMETRIC EM (NPEM) POPULATION PHARMACOKINETIC MODELS

A new program for population modeling has now been developed. It is a combination of a Standard Two Stage (S2S) method which is used first to find the maximum likelihood (ML) parameter values for each subject and the population means and SD's for each parameter. This process is repeated iteratively. With the ranges set by the ML method (mean ± 2-4 SD), the new 3-compartment NPEM program is then run, and the entire joint probability density function (PDF) of the model parameters is computed. Marginal PDF's are displayed for each parameter. The program reads patient data files from the clinical PC programs. One can now make population models having absorptive, central (serum) and peripheral (nonserum) compartments for their own patient populations in community medical centers. With mixed PO and IV dosing, **both V and F** (volume of distribution and bioavailability) can be found. Mean or median parameter values and their SD's can be entered as population values for the clinical MAP Bayesian programs for adaptive control of dosage regimens.

MULTIPLE MODEL LINEAR QUADRATIC (MMLQ) DRUG DOSAGE REGIMENS

A new MMLQ program utilizes the full joint population PDF rather than the single mean or median value for each parameter as is done now using the current MAP Bayesian method. It recognizes that many combinations of possible parameter values exist (the full nonparametric PDF). The MMLQ regimen minimizes the expected value of the squared error in achieving the desired goal (the quadratic cost function, Q) for a linear system (L), having multiple models (MM) of that system. The program has been implemented for a prototype 2 compartment model of lidocaine having 3 values for each parameter, each of which has its own probability, for a total of 3^4, or 81 possible models of the patient.

A MAP Bayesian regimen based on the mean values for each lidocaine parameter (to achieve and maintain a desired serum level goal of 3.0 ug/ml) yielded a tapering infusion regimen of 19.2 mg/min for 5 min, followed by 5.1 mg/min for 15 min, 3.2 mg/min for 30 min, 2.1 mg/min for 1 hour, and by 1.8 mg/min thereafter. However, when this regimen was given to the full set of 3^4 or 81 models of the patient, a wide bandwidth of serum levels ranged from 0.7 to 9.3 ug/ml.

In contrast, the MMLQ regimen yielded an infusion regimen of 12.5 mg/min for 5 min, followed by 3.0 mg/min for 15 min, 2.0 mg/min for 30 min, 1.4 mg/min for 1 hour, and by 1.2 mg/min thereafter. When this regimen was given to the full set of 81 possible models of the patient, the bandwidth of serum levels only ranged from 0.5 to 5.7 ug/ml.

MAP BAYESIAN CLINICAL PROGRAMS FOR INDIVIDUALIZING DRUG DOSAGE

The clinical programs for MAP Bayesian adaptive control of drug dosage employ population models with absorptive, central (serum), and peripheral (nonserum) compartments. The elimination rate constant is linked to clinical descriptors of elimination such as creatinine clearance (many drugs) or cardiac index (lidocaine). Dosage regimens can be designed either to control peak serum concentrations, the peak total body concentration in the peripheral compartment, or desired concentrations in either compartment at any selected time after a dose, by oral, IM, or IV routes. Antibiotic diffusion into simulated endocardial vegetations and bacterial killing curves are now also plotted, linked to the pharmacokinetic models.

The clinical and NPEM programs are available by license from the University. They run on PC's or compatible machines, support VGA color monitors, IBM, Epson, or HP Laserjet printers, and require a math coprocessor 2MB RAM, and DOS 5.0 or more, or OS/2.

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